

1 Claims

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4 1. A method of killing cancer cells, comprising
5 administration to said cells of an effective
6 amount of a c-FLIP inhibitor, wherein the c-
7 FLIP inhibitor is administered as the sole
8 cytotoxic agent in the substantial absence of
9 other cytotoxic agents.

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11 2. A method of treating cancer comprising
12 administration to a subject in need thereof a
13 therapeutically effective amount of a c-FLIP
14 inhibitor, wherein the c-FLIP inhibitor is
15 administered as the sole cytotoxic agent in
16 the substantial absence of other cytotoxic
17 agents.

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19 3. A method of killing cancer cells having a p53
20 mutation, comprising administration to said
21 cells of:
22 (a) a c-FLIP inhibitor and
23 (b) a chemotherapeutic agent, wherein the
24 chemotherapeutic agent is a thymidylate
25 synthase inhibitor, a platinum cytotoxic agent
26 or a topoisomerase inhibitor.

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28 4. A method of treating cancer associated with a
29 p53 mutation comprising administration to a
30 subject in need thereof
31 (a) a c-FLIP inhibitor and
32 (b) a chemotherapeutic agent, wherein the

1 chemotherapeutic agent is a thymidylate
2 synthase inhibitor, a platinum cytotoxic agent
3 or a topoisomerase inhibitor.

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5 5. The method according to claim 3 or claim 4,
6 further comprising administration of:
7 (c) a death receptor binding member.

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9 6. The method according to claim 5, wherein the
10 death receptor is FAS.

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12 7. The method according to claim 6, wherein the
13 binding member is the FAS antibody CH11.

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15 8. The method according to any one of claims 3 to
16 7, wherein the chemotherapeutic agent is 5-FU,
17 oxaliplatin or CPT-11.

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19 9. The method according to claim 8, wherein the
20 chemotherapeutic agent is 5-FU or oxaliplatin.

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22 10. The method according to any one of claims 3 to
23 9, wherein the c-FLIP inhibitor and
24 the chemotherapeutic agent are administered in
25 a potentiating ratio.

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27 11. The method according to claim 10, wherein the
28 c-FLIP inhibitor and
29 the chemotherapeutic agent are administered in
30 concentrations sufficient to produce a CI of
31 less than 0.85.

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1 12. The method according to any one of claims 3 to
2 11, wherein the p53 mutation is such that p53
3 is completely inactivated in the cancer cells.

5 13. The method according to any one of claims 3 to
6 11, wherein the p53 mutation is a missense
7 mutation resulting in the substitution of
8 histidine (R175H mutation) or a missense
9 mutation resulting in the substitution of
10 tryptophan (R248W mutation) for arginine.

12 14. The method according to any one of claims 1 to
13 13, wherein said c-FLIP inhibitor is an RNAi
14 agent, which modulates expression of a c-FLIP
15 gene.

17 15. The method according to claim 14 wherein the
18 c-FLIP inhibitor is an RNAi agent having
19 nucleotide sequence
20 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
21 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2)

23 16. The use of a c-FLIP inhibitor as the sole
24 cytotoxic agent in the preparation of a
25 medicament for treating cancer, wherein the
26 medicament is for treatment in the substantial
27 absence of other cytotoxic agents.

29 17. The use of
30 (a) a c-FLIP inhibitor and
31 (b) a chemotherapeutic agent, wherein the
32 chemotherapeutic agent is a thymidylate

1 synthase inhibitor, a platinum cytotoxic agent
2 or a topoisomerase I inhibitor
3 in the preparation of a medicament for
4 treating cancer associated with a p53
5 mutation.

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7 18. The use according to claim 17, wherein the
8 medicament further comprises:
9 (c) a death receptor binding member.

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11 19. The use according to claim 18, wherein the
12 death receptor is FAS.

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14 20. The use according to claim 19, wherein the
15 binding member is the FAS antibody CH11.

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17 21. The use according to any one of claims 17 to
18 20, wherein the chemotherapeutic agent is 5-
19 FU, oxaliplatin or CPT-11.

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21 22. The use according to claim 21, wherein the
22 chemotherapeutic agent is 5-FU or oxaliplatin.

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24 23. The use according to any one of claims 17 to
25 21, wherein the c-FLIP inhibitor and
26 the chemotherapeutic agent are present in a
27 potentiating ratio.

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29 24. The use according to claim 23, wherein the c-
30 FLIP inhibitor and the chemotherapeutic agent
31 are present in concentrations sufficient to

1 produce a CI of less than 0.85.

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3 25. The use according to any one of claims 17 to
4 24, wherein the p53 mutation is such that p53
5 is completely inactivated in the cancer cells.

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7 26. The use according to any one of claims 17 to
8 24, wherein the p53 mutation is a missense
9 mutation resulting in the substitution of
10 histidine (R175H mutation) or a missense
11 mutation resulting in the substitution of
12 tryptophan (R248W mutation) for arginine.

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14 27. The use according to any one of claims 16 to
15 26, wherein said c-FLIP inhibitor is an RNAi
16 agent, which modulates expression of a c-FLIP
17 gene.

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19 28. The use according to claim 27 wherein the c-
20 FLIP inhibitor is an RNAi agent having
21 nucleotide sequence
22 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
23 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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26 29. A pharmaceutical composition for the treatment
27 of cancer, wherein the composition comprises a
28 c-FLIP inhibitor as the sole cytotoxic agent
29 and a pharmaceutically acceptable excipient,
30 diluent or carrier, wherein the composition is
31 for treatment in the absence of other
32 cytotoxic agents.

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2 30. A pharmaceutical composition for the treatment
3 of a cancer associated with a p53 mutation,
4 wherein the composition comprises (a) a c-FLIP
5 inhibitor
6 (b) a chemotherapeutic agent, wherein the
7 chemotherapeutic agent is a thymidylate
8 synthase inhibitor, a platinum cytotoxic agent
9 or a topoisomerase I inhibitor
10 and
11 (c) a pharmaceutically acceptable excipient,
12 diluent or carrier.
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14
15 31. The composition according to claim 30, further
16 comprising (c) a death receptor binding
17 member.
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19 32. The composition according to claim 31, wherein
20 the death receptor is FAS.
21
22 33. The composition according to claim 32, wherein
23 the binding member is the FAS antibody CH11.
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25 34. The composition according to any one of claims
26 30 to 33, wherein the chemotherapeutic agent
27 is 5-FU, oxaliplatin or CPT-11.
28
29 35. The composition according to claim 34, wherein
30 the chemotherapeutic agent is 5-FU or
31 oxaliplatin.
32

- 1 36. The composition according to any one of claims
2 30 to 36, wherein the c-FLIP inhibitor and
3 the chemotherapeutic agent are present in a
4 potentiating ratio.
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- 6 37. The composition according to claim 36, wherein
7 the c-FLIP inhibitor and
8 the chemotherapeutic agent are present in
9 concentrations sufficient to produce a CI of
10 less than 0.85.
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- 12 38. The composition according to any one of claims
13 30 to 37, wherein the p53 mutation is such
14 that p53 is completely inactivated in the
15 cancer cells.
16
- 17 39. The composition according to any one of claims
18 30 to 37, wherein the p53 mutation is a
19 missense mutation resulting in the
20 substitution of histidine (R175H mutation) or
21 a missense mutation resulting in the
22 substitution of tryptophan (R248W mutation)
23 for arginine.
24
- 25 40. The composition according to any one of claims
26 29 to 39, wherein said c-FLIP inhibitor is an
27 RNAi agent, which modulates expression of a c-
28 FLIP gene.
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- 30 41. The composition according to claim 40 wherein
31 the c-FLIP inhibitor is an RNAi agent having
32 nucleotide sequence

1 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
2 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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5 42. A kit for the treatment of cancer associated
6 with a p53 mutation, said kit comprising
7 (a) a c-FLIP inhibitor and
8 (b) a chemotherapeutic agent, wherein the
9 chemotherapeutic agent is a thymidylate
10 synthase inhibitor, a platinum cytotoxic agent
11 or a topoisomerase I inhibitor and
12 (c) instructions for the administration of (a)
13 and (b) separately, sequentially or
14 simultaneously.

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17 43. An RNAi agent having nucleotide sequence
18 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
19 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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22 44. An RNAi agent consisting of nucleotide
23 sequence
24 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
25 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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